Physiotherapy use and access-barriers in persons with multiple sclerosis: A cross-sectional analysis

Fortunato, Remo ; van der Maas, Nico Arie ; Biland-Thommen, Ursula ; Kaufmann, Marco ; Sieber, Chloé ; Kamm, Christian P ; Zecca, Chiara ; Gobbi, Claudio ; Chan, Andrew ; Calabrese, Pasquale ; Kesselring, Jürg ; von Wyl, Viktor

Abstract: Introduction: Physiotherapy may alleviate many multiple sclerosis (MS) symptoms, yet very little is known about physiotherapy accessibility and possible barriers in persons with MS (pwMS). We therefore aimed to elucidate physiotherapy use and possible access-barriers using data from 1493 pwMS from the Swiss Multiple Sclerosis Registry (SMSR), a patient-centered, longitudinal, observational MS study. Methods: We used data of the SMSR to investigate the question at hand in a multivariable logistic regression model with regularly receiving physiotherapy (yes/no) as the outcome. Potential explanatory variables were investigated following an AIC-driven model selection approach and consisted of a priori specified socio-demographic variables, health status, and personal or social mobility variables. As a last step, the impact of physiotherapist supply on regular use was assessed in the final model. Missing data were handled by multiple imputation (main analysis), and complete case sensitivity analyses were performed. Results: The main analysis included 1493 participants. In the multivariable logistic regression, positive associations were found between the use of physiotherapy and the following variables: having a primary-progressive MS (Odds Ratio (OR) [95% Confidence Intervals] 1.97 [1.18; 3.29]), being more severely impaired (EDSS 4-6.5 OR 1.84 [1.16; 2.91]), higher number of current symptoms (1 OR 3.31 [1.63; 6.74], 2-3 OR 3.43 [1.8; 6.53], 4-5 OR 4.44 [2.28; 8.66], 6-7 OR 4.06 [1.90; 8.70], 8-9 OR 3.87 [1.71; 8.75], being on disability pension (OR 1.75 [1.24; 2.46], or having applied for it OR 2.25 [1.31; 3.85]), having gait problems (OR 1.58 [1.11; 2.23]), having been in a rehabilitation clinic in the past 12 months (OR 4.43 [2.17; 9.03]), and currently being on disease-modifying treatment (OR 1.61 [1.12; 2.31]). Negative associations were found for a higher quality of life (OR 0.92 [0.85; 0.98]), working more than 80% (OR 0.47 [0.30; 0.75]) and being from the French language region (OR 0.66 [0.47; 0.94]). No association between physiotherapist supply and regular physiotherapy use was detected. Discussion: In a large, Swiss-based MS population, little evidence for socio-demographic barriers to physical therapy was found. Physiotherapy uptake was higher among pwMS with more impairments, lower health-related quality of life, or who have been discharged recently from inpatient rehabilitation. The uptake differences by language region warrant further investigations.

DOI: https://doi.org/10.1016/j.msard.2020.102710

Originally published at:
Fortunato, Remo; van der Maas, Nico Arie; Biland-Thommen, Ursula; Kaufmann, Marco; Sieber, Chloé; Kamm, Christian P; Zecca, Chiara; Gobbi, Claudio; Chan, Andrew; Calabrese, Pasquale; Kesselring, Jürg; von Wyl, Viktor (2021). Physiotherapy use and access-barriers in persons with multiple sclerosis: A cross-sectional analysis. Multiple Sclerosis and Related Disorders, 48:102710.
DOI: https://doi.org/10.1016/j.msard.2020.102710

Multiple Sclerosis and Related Disorders 48 (2021) 102710

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Physiotherapy use and access-barriers in persons with multiple sclerosis: A cross-sectional analysis

Remo Fortunato [a,j], Nico Arie van der Maas [b], Ursula Biland-Thommen [c], Marco Kaufmann [a], Chloé Sieber [a], Christian P Kamm [d,e], Chiara Zecca [f,g], Claudio Gobbi [f,g], Andrew Chan [d], Pasquale Calabrese [h], Jürg Kesselring [i], Viktor von Wyl [a,*], for the Swiss Multiple Sclerosis Registry

[a] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Hirschengraben 84, 8001 Zurich, Switzerland
[b] Institut für Physiotherapieforschung, Lindenweg 48, 2503 Biel, Switzerland
[c] Neurophysio biland/kestenholz, Poststrasse 6, 4460 Gelterkinden, Switzerland
[d] Department of Neurology, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland
[e] Neurocentre, Luzerner Kantonsspital, Lucerne, Switzerland
[f] Faculty of biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland
[g] Department of Neurology, Multiple Sclerosis Center (MSC), Neurocenter of Southern Switzerland, Lugano, Switzerland
[h] Division of Molecular and Cognitive Neuroscience, University of Basel, Basel, Switzerland
[i] Department of Neurology and Neurorehabilitation, Rehabilitation Center, Valens, Switzerland
[j] Department of Health Sciences and Technology, ETH Zurich, Zürich, Switzerland

A B S T R A C T

Introduction: Physiotherapy may alleviate many multiple sclerosis (MS) symptoms, yet very little is known about physiotherapy accessibility and possible barriers in persons with MS (pwMS). We therefore aimed to elucidate physiotherapy use and possible access-barriers using data from 1493 pwMS from the Swiss Multiple Sclerosis Registry (SMSR), a patient-centered, longitudinal, observational MS study.

Methods: We used data of the SMSR to investigate the question at hand in a multivariable logistic regression model with regularly receiving physiotherapy (yes/no) as the outcome. Potential explanatory variables were investigated following an AIC-driven model selection approach and consisted of a priori specified socio-demographic variables, health status, and personal or social mobility variables. As a last step, the impact of physiotherapist supply on regular use was assessed in the final model. Missing data were handled by multiple imputation (main analysis), and complete case sensitivity analyses were performed.

Results: The main analysis included 1493 participants. In the multivariable logistic regression, positive associations were found between the use of physiotherapy and the following variables: having a primary-progressive MS (Odds Ratio (OR) [95% Confidence Intervals] 1.97 [1.18; 3.29]), being more severely impaired (EDSS 4-6.5 OR 1.84 [1.16; 2.91]), higher number of current symptoms (1 OR 3.31 [1.63; 6.74], 2-3 OR 3.43 [1.8; 6.53], 4-5 OR 4.44 [2.28; 8.66], 6-7 OR 4.06 [1.90; 8.70], 8-9 OR 3.87 [1.71; 8.75], being on disability pension (OR 1.75 [1.24; 2.46], or having applied for it OR 2.25 [1.31; 3.85]), having gait problems (OR 1.58 [1.11; 2.23]), having been in a rehabilitation clinic in the past 12 months (OR 4.43 [2.17; 9.03]), and currently being on disease-modifying treatment (OR 1.61 [1.12; 2.31]). Negative associations were found for a higher quality of life (OR 0.92 [0.85; 0.98]), working more than 80% (OR 0.47 [0.30; 0.75]) and being from the French language region (OR 0.66 [0.47; 0.94]). No association between physiotherapist supply and regular physiotherapy use was detected.

Discussion: In a large, Swiss-based MS population, little evidence for socio-demographic barriers to physical therapy was found. Physiotherapy uptake was higher among pwMS with more impairments, lower health-related quality of life, or who have been discharged recently from inpatient rehabilitation. The uptake differences by language region warrant further investigations.

1. Background

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system, with onset in early adulthood, affecting approximately 15,000 people in Switzerland and over 2 million worldwide (Kaufmann et al., 2019; Vos et al., 2016).

While disease-modifying treatments (DMT) are essential to minimize axonal damage and loss, as well as the relapse rate, there is currently still no curative treatment for MS. In addition, drugs that ameliorate clinical symptoms are sparse (Toosy et al., 2014). Therefore, existing symptoms must be managed with symptomatic forms of therapy such as physical and occupational therapies.

* Corresponding author.
E-mail address: viktor.vonwyl@uzh.ch (V. von Wyl).

https://doi.org/10.1016/j.msard.2020.102710
Received 19 June 2020; Received in revised form 8 December 2020; Accepted 20 December 2020
Available online 23 December 2020

Physiotherapy is recommended for the treatment of MS, since there is strong evidence that it helps to improve quality of life (QoL) as well as to maintain mobility (Alphonsus et al., 2019; Khan and Amatya, 2017). Furthermore, physiotherapy alleviates gait problems (Henze et al., 2017; Khan and Amatya, 2017; Wiles et al., 2001) and reduces bladder problems, in particular through pelvic floor exercises (Block et al., 2015; Henze, 2004; Henze et al., 2018a; Kesselring and Beer, 2005). Moreover, there is some evidence that physiotherapy may improve balance (Khan and Amatya, 2017; Paltamaa et al., 2012; Wiles et al., 2001), ameliorate spasticity (Henze, 2004), and reduce pain (in particular shoulder, neck, joint and back pain) (Henze, 2004). In addition, there is strong evidence for physiotherapy being able to reduce fatigue (Henze et al., 2018b; Kesselring and Beer, 2005; Khan and Amatya, 2017). All these symptoms have been shown to reduce QoL and are all common in people with MS (Barin et al., 2018).

Despite proven benefits, uptake of physiotherapy is not universal in Switzerland and other countries. As shown by an earlier study, as many as 43% of the participants in the Swiss MS Registry reported to receive physiotherapy on a regular basis. (Barin et al., 2019). Studies to investigate possible reasons for limited physiotherapy access or uptake have been performed in other countries, but not in Switzerland. For example, Campbell et al. reported that physiotherapy access for pwMS is mostly hindered by mobility, fatigue, continence and transport issues and the need of attendance (Campbell et al., 2017). Additionally, distance to travel, pain, difficulty with wheelchair transfers, poor availability of physiotherapy-services, work and family commitments and depression, had been reported as potential barriers (Campbell et al., 2017). By contrast, Finlayson et al. further reported that living in an urban or suburban community, a deteriorating MS status, experiencing problems with spasticity, having transfer difficulties in the living environment, being hospitalized in the past 6 months, and seeing a family physician, were positively associated with recent use of physiotherapy services (Finlayson et al., 2010). Furthermore, Milivojevic et al. found, that pwMS who used rehabilitation had higher levels of impairment compared to those without (Milivojević et al., 2013).

However, there are also notable differences between the health systems included in these earlier studies and the Swiss setting. Switzerland has a mandatory health insurance system with nearly universal access to care, but high out-of-pocket costs and deductibles (Osborn et al., 2016). Physiotherapy is reimbursed by mandatory health insurance, if it is prescribed by a physician. However, prescriptions are usually limited to 9 sessions after which a new prescription is necessary. This can be renewed up to a total of 36 sessions yearly. Severely affected patients may receive long-term treatment over many years. For such long-term treatments, cost approval by the health insurance is required.

Given the knowledge gaps about care access barriers for physiotherapy in Switzerland, our objective was to identify factors that hinder or facilitate the use of physiotherapy. Furthermore, we aimed to investigate whether the availability of physiotherapists has an effect on physiotherapy use.

2. Methods

2.1. Participants and data analysis

We analyzed data from the Swiss Multiple Sclerosis Registry (SMSR), which also assessed the use of physiotherapy in persons with MS. The SMSR is a prospective, observational, patient-centered, ongoing study including adults with MS living in Switzerland. This study obtains data directly from the participants with MS by online and paper questionnaires, that is, information is based on self-reports. To ensure disease status, participants are required to submit a diagnosis confirmation filled out by their treating physician. Detailed information on study population and recruitment procedures have been published elsewhere (Puhan et al., 2018; Steinemann et al., 2018). The data used for this project are cross-sectional and based on the first questionnaire patients complete to enter the study (baseline questionnaire), assessed between June 2016 and April 2019.

The Swiss Multiple Sclerosis Registry has been approved by the Ethics Committee of the Canton of Zurich (PB-2016-00,894), including the use of the registry data for the present study (KEK 2019-01027). Written informed consent has been obtained from all SMSR participants (Steinemann et al., 2018).

To acquire a quantitative measure of physiotherapy supply, a proxy for physiotherapy availability, we used the ZIP codes of the 4057 physiotherapists and clinics who reported offering general physiotherapy and were registered on the Physioswiss website (https://www.physioswiss.ch/de/practices). We then used population count data from the Federal Statistical Office to calculate the number of therapists per 10'000 inhabitants in each ZIP code area.

2.2. Statistical analysis

The outcome of interest was, whether pwMS "regularly used physiotherapy" (wording in questionnaire). In Switzerland, physiotherapy for pwMS is mainly provided in dedicated physiotherapy practices, but to some extent also as home-based physiotherapy or in out-patient facilities of clinics. The groups with and without physiotherapy were compared descriptively by use of means for continuous and percentages for categorical variables. Moreover, to identify factors associated with physiotherapy use, a multivariable logistic regression model was built following an AIC-driven model selection algorithm with physiotherapy use as outcome. The model was built as follows:

First, the following variables were defined as confounders: sex, age, MS type, an EDSS proxy measure based on self-reported walking distances (0-3.5; 4-6.5; 7-9.5) (Kaufmann et al., 2020), education level and smoking. These variables were included as fixed variables in all fitted models, since they correlate with disease severity and health-conscious behavior, as well as language region (representing cultural differences between parts of Switzerland), which influences healthcare use (Supplementary Table 1).

Second, a pre-specified set of variables of interest was defined, reflecting previously published, possible care access barriers: BMI, number of MS-symptoms, incontinence, gait problems, fatigue, pain, paralysis, weakness, balance problems, dizziness, work percent, disability pension, ability to drive, ability to use public transport, area type of residence, living situation, alcohol consumption and being in a wheelchair, all as categorical variables. In addition, time since diagnosis and health related quality of life as assessed by the EuroQol 5 Dimension instrument (EQ5D) were added as continuous variables.

Third, a stepwise approach was followed by fitting a confounder-adjusted model adding only one variable of the predefined variable-set at a time. The model with the lowest Akaike information criterium (AIC) was then maintained and considered the new reference model in case of a decrease of 2 units or greater compared to the previous reference model (Faraway, 2002). Thereafter, the variable newly included in the model was removed from the set of potential variables and the process repeated, starting with the new reference model. The process ended once no variable further reduced the AIC by at least two units. Another description of this process can also be found in a previous study (Barin et al., 2019).

Forth, using the final model from step 3, the following exploratory variables were examined following the same stepwise approach: citizenship, changed nutrition, having any comorbidities, memory symptoms, sexual symptoms, epilepsy, gastrointestinal symptoms, tremor, spasms, paresthesia, dysphagia, language impairments, visual symptoms, depression, other symptoms not specified, disease-modifying treatment DMT, side effects, use of alternative medicine, lifestyle changes upon diagnosis, physical activity, having children and having been in a clinic for rehabilitation.

To investigate any effect of physiotherapy availability on physiotherapy use, the measure of supply (availability of physiotherapists per

10'000 inhabitants in a given region, categorized into quintiles) was added to the final, multivariable model.

The model was developed on the basis of a dataset with imputation of missing values for variables of interest using multiple imputation by chained equations and the models run on the imputed dataset (Rubin, 1996; White et al., 2011). As a sensitivity analysis, the results based on the imputed dataset were compared to the results in the complete case scenario. All statistical analyses were done using STATA version 16 (Stata Corp. College Station, TX, USA).

2.3. Results

The patient selection process for this study is illustrated in Fig. 1. This study included 1493 participants, of which 693 [46.4%] regularly attended physiotherapy; 800 [53.6%] were not receiving physiotherapy. The overall median age was 48 years and 72.7% were females (not shown). Moreover, 3% had a clinically isolated syndrome (CIS), 10% primary progressive MS (PPMS), 68% relapsing-remitting MS (RRMS) and 17% secondary progressive MS (SPMS).

As shown in Table 1 and Supplementary Table 2, several factors differed substantially between persons with and without uptake of physiotherapy. In particular, physiotherapy uptake was higher among persons with primary progressive MS, an EDSS proxy measure greater than 4, a longer time since diagnosis, a greater number of symptoms, and a lower health-related quality of life, as well as in persons who are not working or who are on disability pension.

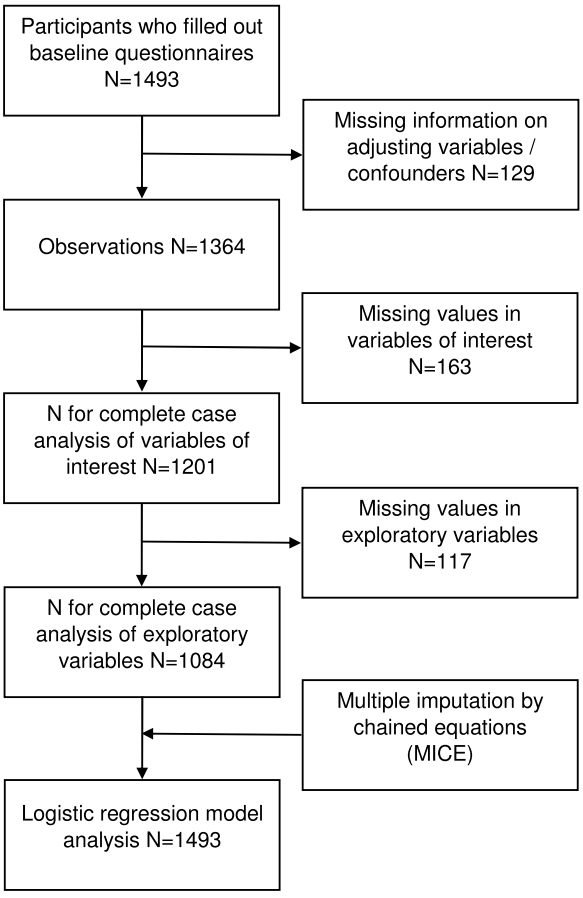

Fig. 1. N, number; Study Flowchart. Displayed are the number of participants, also referred to as observations, and the number of exclusions due to missing values, leading to the number of cases included in the complete case analyses, which were used to build the model and later for the sensitivity analysis. Thereafter multiple imputation by chained equations was performed for the final analysis. The complete case models were also used for a sensitivity analysis.

Table 1
Characteristics of persons with multiple sclerosis with and without regular use of physiotherapy.

	Physiotherapy			
Variable	No		Yes	
N	800	53.6%	693	46.4%
Sex (=Female)	607	75.9%	479	69.1%
Age (mean)	43		52	
BMI (mean)	24.85		25.04	
Language region				
German	617	77.1%	557	81.2%
French	148	18.5%	109	15.9%
Italian	35	4.4%	20	2.9%
Highest education level				
Up to mandatory school	30	3.9%	30	4.6%
Apprenticeship	306	40.8%	294	44.7%
Highschool	68	9.1%	58	8.8%
Higher professional education	115	15.3%	108	16.4%
University / University of applied sciences	231	30.8%	167	25.4%
MS type				
CIS	39	5.0%	5	0.7%
PPMS	37	4.7%	119	17.3%
RRMS	648	82.9%	369	53.6%
SPMS	58	7.4%	196	28.4%
EDSS proxy				
0-3.5	673	84.1%	314	45.3%
4-6.5	39	4.9%	174	25.1%
7-9.5	12	1.5%	91	13.1%
Time since diagnosis in years (mean)	8		13	
Number of current symptoms				
None	188	23.5%	14	2.0%
1	119	14.9%	31	4.5%
2-3	194	24.3%	94	13.6%
4-5	133	16.6%	161	23.2%
6-7	65	8.1%	129	18.6%
8-9	46	5.8%	133	19.2%
>10	55	6.9%	131	18.9%
Disease modifying treatment (DMT)	595	77.8%	457	70.5%
EQ5D-Index (mean)	0.86		0.68	
Working				
Not	205	26.8%	371	54.2%
<50%	100	13.1%	120	17.5%
50-80%	203	26.5%	137	20.0%
>80%	258	33.7%	56	8.2%
Disability pension				
No	593	77.2%	239	35.3%
Yes	141	18.4%	373	55.0%
Applied for	34	4.4%	66	9.7%
Able to drive				
No	71	9.2%	175	25.5%
Yes	632	81.7%	388	56.6%
Yes, modified car	7	0.9%	67	9.8%
No drivers license	64	8.3%	55	8.0%
Able to use public transport	742	95.9%	538	78.9%
Typology residential area				
Urban	474	60.2%	392	57.8%
Sub-urban	190	24.1%	159	23.5%
Rural	123	15.6%	127	18.7%
Wheelchair	28	3.5%	215	31.0%
Any comorbidities	187	23.4%	258	37.2%
Having children	408	56.7%	437	69.8%
Rehabilitation clinic stay in past 12 months	11	1.4%	132	19.0%

BMI: Body Mass Index; CIS: Clinically isolated syndrome; EDSS: Expanded disability status scale; EQ5D: EuroQol 5 dimensions; MS: Multiple sclerosis; PPMS: Primary-progressive MS; RRMS: Relapsing-remitting MS; SPMS: Secondary-progressive MS.

As displayed in Table 2, factors positively associated with use of physiotherapy were primary-progressive MS (OR 1.97 [1.18; 3.29]), being more severely impaired (EDSS 4-6.5 OR 1.84 [1.16; 2.91]), having a higher number of current symptoms (1 OR 3.31 [1.63; 6.74], 2-3 OR 3.43 [1.80; 6.54], 4-5 OR 4.44 [2.28; 8.66], 6-7 OR 4.06 [1.90; 8.70], 8-9 OR 3.87 [1.71; 8.75]), being on disability pension (OR 1.75 [1.24; 2.46], or having applied for disability pension OR 2.25 [1.31; 3.85]),

Table 2
Confounder adjusted logistic regression model for the full sample to identify factors associated with physiotherapy use in persons with multiple sclerosis. Effect sizes that reached statistical significance ($p<0.05$) are indicated in bold. (A graph with depiction of the confidence intervals can be found in the appendix as supplementary Fig. 1)

Variable	OR	Physiotherapy [=Yes] CI [95%]
Sex (Female)	1.16	[0.83; 1.63]
Age	1.05	[0.98; 1.12]
MS type		
CIS	0.59	[0.21; 1.65]
PPMS	**1.97**	**[1.18; 3.29]**
RRMS	ref.	
SPMS	1.23	[0.77; 1.96]
EDSS proxy		
0-3.5	ref.	
4-6.5	**1.84**	**[1.16; 2.91]**
7-9.5	1.77	[0.77; 4.06]
Highest education level		
Up to mandatory school	0.75	[0.38; 1.47]
Apprenticeship	ref.	
Highschool	0.89	[0.53; 1.49]
Higher professional education	1.33	[0.88; 2.01]
University / University of applied sciences	1.20	[0.86; 1.69]
Language region		
German	ref.	
French	**0.66**	**[0.47; 0.94]**
Italian	0.61	[0.3; 1.25]
Smoker		
Never	ref.	
Former	1.25	[0.92; 1.71]
Current	0.96	[0.67; 1.37]
EQ5D-index		
(per index point increase)	**0.92**	**[0.85; 0.98]**
Number of symptoms		
None	ref.	
1	**3.31**	**[1.63; 6.74]**
2-3	**3.43**	**[1.8; 6.53]**
4-5	**4.44**	**[2.28; 8.66]**
6-7	**4.06**	**[1.9; 8.7]**
8-9	**3.87**	**[1.71; 8.75]**
>10	1.86	[0.77; 4.51]
Working		
Not	ref.	
<50%	1.16	[0.76; 1.76]
50-80%	0.92	[0.64; 1.34]
>80%	**0.47**	**[0.3; 0.75]**
Disability pension		
No	ref.	
Yes	**1.75**	**[1.24; 2.46]**
Applied for	**2.25**	**[1.31; 3.85]**
Gait problems	**1.58**	**[1.11; 2.23]**
Able to drive		
No	ref.	
Yes	0.81	[0.53; 1.22]
Yes modified Car	2.13	[0.83; 5.44]
No driver's license	0.78	[0.44; 1.39]
Pain	1.33	[0.95; 1.88]
Rehabilitation clinic	**4.43**	**[2.17; 9.03]**
Spasms	**2.05**	**[1.46; 2.89]**
Disease-modifying treatment	**1.61**	**[1.12; 2.31]**
Observations		**1493**

CIS: Clinically isolated syndrome; EDSS: Expanded disability status scale; EQ5D: EuroQol 5 dimensions; MS: Multiple sclerosis; PPMS: Primary-progressive MS; RRMS: Relapsing-remitting MS; SPMS: Secondary-progressive MS.

gait problems (OR 1.58 [1.11; 2.23]), having been in a clinic for rehabilitation in the past 12 months (OR 4.43 [2.17; 9.03]), spasms (OR 2.05 [1.46; 2.89]) and currently being on disease-modifying treatment (OR 1.61 [1.12; 2.31]). A negative association was found for living outside the German-speaking part of Switzerland (French-speaking 0.66 [0.47; 0.94]), a higher health-related quality of life (EQ5D OR 0.92 [0.85; 0.98]) and working more than 80% (OR 0.47 [0.30; 0.75]). The sensitivity analysis based on the complete case logistic regression yielded similar results as the main analysis.

Furthermore, we studied whether the region-specific per-capita number of physiotherapists was associated with physiotherapy uptake by adding a quantitative measure of supply to the logistic regression presented in Table 2. This index of physiotherapy supply variable did not demonstrate an association with increased physiotherapy uptake. Moreover, the effect sizes for language region remained nearly unchanged (results shown in Supplementary Table 3).

3. Discussion

By analyzing data from 1493 participants of the Swiss MS Registry, several factors were identified to be associated with an increased uptake of physiotherapy, namely a higher EDSS (as measured by the proxy), lower quality of life (EQ5D), having more MS-symptoms, being on disability pension, gait problems, spasms and having been in a clinic for rehabilitation in the past 12 months. By contrast, other variables previously implicated with care access barriers such as lower education or inability to drive did not reach statistical significance, or did not even enter the final model (e.g. ability to use public transport or degree of urbanity of home location). Furthermore, the supply of physiotherapists, expressed as number of physiotherapy providers per capita and divided into quintiles, was not associated with uptake.

These findings suggest that the most important driver of physiotherapy use is the impact on health-related quality of life by the disease (e.g., expressed the EQ-5D index) and the impairments (particularly gait problems or spasms). Nevertheless, physiotherapy use differed by language regions, but those differences were independent of supply of physiotherapists per capita. Therefore, it could be speculated that not supply but referral and prescription practices of physicians may be somewhat different in non-German language regions of Switzerland. However, there is currently no evidence to support this or any alternative explanation for language region differences of physiotherapy uptake in Switzerland.

Our results indicate that an increase of symptoms and its consequences in daily life are the main drivers for the uptake of physiotherapy. Recent studies propose that exercise in MS may be viewed as a preventive and disease-modifying measure. It has been suggested that an early physiotherapy initiation, including strength and endurance exercises, might change the course of MS. (Riemenschneider et al 2018, Dalgas et al 2019) However, our results do not support that the proposed paradigm shift has happened in Switzerland yet.

Unlike in several other countries, little evidence could be found for systematic access-barriers on a population level. Therefore, this suggests that physiotherapy supply and access are in general quite good in Switzerland, which also corresponds to the view of many practitioners. However, access-barriers on an individual level may exist. For example, it is known for Switzerland that high out-of-pocket expenditures such as insurance deductibles can be prohibitive for accessing care. Because our data do not include insurance characteristics or income, we are unable to perform individual-level analyses into these aspects. Nonetheless, there are several other obstacles acting at the individual level that might have influenced our findings: lack of compatibility with vocational/working duties, avoiding to be confronted with symptoms and the fear to be stigmatized, lack of awareness about preventive effects of physiotherapeutic treatment, fatigue and exhaustion in working individuals, but also the tendency to underreport minor physical deficits that might necessitate physiotherapeutic intervention and finally, the lack of availability of attendance are altogether personal and circumstantial variables that might impede a person with MS to claim for and to utilize physiotherapeutic supply.

Comparisons with studies performed in different health care settings, such as the UK, are difficult. The health system differences may at least partially explain why there is little consistency between our findings and those of the survey conducted by Campbell et al. (2017). For example, we did not find any evidence in support of lack of mobility, fatigue,

continence issues, transport issues or the patient needing someone to go with them hindering physiotherapy use on a population level. This could be due to two factors: One being that the UK study was conducted in persons with PPMS, while our study included all MS types, most of which with a RRMS. The other being that the UK study was a questionnaire specifically asking pwMS about access-barriers, thus assessing this topic more on an individual level, while we were investigating access-barriers on a population level.

Notable strengths of our study are: Its comparatively large sample size (Calabrese et al., 2017; Campbell et al., 2017) and the inclusion of persons across the full MS disease spectrum (including newly diagnosed and persons with progressive MS). This was enabled by the provision of paper and online questionnaires in three national languages, as well as the broad support and communication of the Swiss Multiple Sclerosis Society. Furthermore, we were able to cover a comprehensive battery of variables on geographic, socio-demographic, and MS-related factors (Puhan et al., 2018). However, some limitations need to be mentioned, namely a lack of information on participants financial situations and health insurance status, as well as the fact that all the variables were self-reported and therefore prone to the known biases (e.g. recall or underreporting bias). While certain variables intuitively appear to be closely related, no problems of multicollinearity were detected. Furthermore, in the analysis of physiotherapist density, we were unable to consider the specialty of physiotherapists.

To summarize, our study has found little evidence for physiotherapy access-barriers on a population level in people with MS living in Switzerland, a setting with universal access to health care.

Accordingly, use of physiotherapy was primarily driven by health status, namely pwMS with a higher disability and lower health-related quality of life. Furthermore, having been in a rehabilitation clinic in the past 12 months also stood out as a driving factor for use of outpatient physiotherapy. Physiotherapy is a standard treatment in inpatient rehabilitation. Upon discharge, persons with MS are often directly referred to physiotherapists and advised to continue the exercise programs. There were also indications of physiotherapy uptake differences between the German and the French and Italian language regions. Whether these regional differences will be confirmed, and if these are rooted in cultural aspects, different collaboration and referral models between neurologists and physiotherapists, or other as of yet unknown factors warrants further investigation.

Funding

The authors wish to thank the Swiss Multiple Sclerosis Society for funding the Swiss MS Registry (SMSR). The funder had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Remo Fortunato: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing - original draft, Visualization, Project administration. **Nico Arie van der Maas:** Conceptualization, Investigation, Resources, Writing - review & editing. **Ursula Biland-Thommen:** Conceptualization, Investigation, Resources, Writing - review & editing. **Marco Kaufmann:** Conceptualization, Methodology, Software, Resources, Data curation, Writing - review & editing. **Chloé Sieber:** Investigation, Resources, Writing - review & editing. **Christian P Kamm:** Investigation, Resources, Writing - review & editing. **Chiara Zecca:** Investigation, Resources, Writing - review & editing. **Claudio Gobbi:** Investigation, Resources, Writing - review & editing. **Andrew Chan:** Investigation, Resources, Writing - review & editing. **Pasquale Calabrese:** Investigation, Resources, Writing - review & editing. **Jürg Kesselring:** Investigation, Resources, Writing - review & editing. **Viktor von Wyl:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

CPK has received honoraria for lectures as well as research support from Biogen, Novartis, Almirall, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche, Eli Lilly, Celgene and the Swiss MS Society (SMSG).

CG The Department of Neurology, Regional Hospital Lugano (EOC), Lugano, Switzerland, receives financial support from Teva, Merck Serono, Biogen, Genzyme, Roche, Celgene, Bayer, and Novartis. The submitted work is not related to these agreements.

CZ has received compensation for consulting services and for speaking activities from Biogen, Merck, Mylan, Novartis, Teva, Roche, and Sanofi Genzyme.

PC has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from: Abbvie, Actelion, Almirall, Bayer-Schering, Biogen Idec, EISAI, Disease burden of MS Genzyme, Lundbeck, Merck Serono, Novartis, Pfizer, Teva, and Sanofi-Aventis; his research is also supported by the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation and the SOFIA Foundation.

RF, MK, CS, JK, and VvW declare that there is no conflict of interest.

Acknowledgments

We thank the study participants who not only contributed data but who are also absolutely instrumental in all aspects of study design and conduct of the SMSR. We further thank the members of the SMSR Data Centre at the Epidemiology, Biostatistics & Prevention Institute of the University of Zurich and the Swiss Multiple Sclerosis Cohort Study for the excellent collaboration.

Members of the Swiss Multiple Sclerosis Registry are: Bernd Anderseck, Pasquale Calabrese, Andrew Chan, Claudio Gobbi, Roger Häussler, Christian P. Kamm, Susanne Kägi, Jürg Kesselring (President), Jens Kuhle (Chair of Clinical and Laboratory Research Committee), Roland Kurmann, Christoph Lotter, Andreas Lutterotti, Kurt Luyckx, Zina-Mary Manjaly, Patricia Monin, Stefanie Müller, Krassen Nedeltchev, Caroline Pot, Milo A. Puhan, Irene Rapold, Anke Salmen, Klaas Enno Stephan, Claude Vaney (Chair of Patient- and Population Research Committee), Viktor von Wyl (Chair of IT and Data Committee), Chiara Zecca.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2020.102710.

References

Alphonsus, K.B., Su, Y., D'Arcy, C., 2019. The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: systematic review and meta-analysis. Complement. Ther. Med. 43, 188–195. https://doi.org/10.1016/j.ctim.2019.02.010.

Barin, L., Kaufmann, M., Salmen, A., Kamm, C.P., Gobbi, C., Kuhle, J., Pot, C., Chan, A., Czaplinski, A., Ajdacic-Gross, V., Rodgers, S., Kesselring, J., Puhan, M.A., von Wyl, V., 2019. Patterns of care for Multiple Sclerosis in a setting of universal care access: a cross-sectional study. Mult. Scler. Relat. Disord. 28, 17–25. https://doi.org/10.1016/j.msard.2018.11.033.

Barin, L., Salmen, A., Disanto, G., Babačić, H., Calabrese, P., Chan, A., Kamm, C.P., Kesselring, J., Kuhle, J., Gobbi, C., Pot, C., Puhan, M.A., von Wyl, V., 2018. The disease burden of Multiple Sclerosis from the individual and population perspective: which symptoms matter most? Mult. Scler. Relat. Disord. 25, 112–121. https://doi.org/10.1016/j.msard.2018.07.013.

Block, V., Rivera, M., Melnick, M., Allen, D.D., 2015. Do physical therapy interventions affect urinary incontinence and quality of life in people with multiple sclerosis? Int. J. MS Care 17, 172–180. https://doi.org/10.7224/1537-2073.2014-031.

Calabrese, P., Kobelt, G., Berg, J., Capsa, D., Eriksson, J., 2017. New insights into the burden and costs of multiple sclerosis in Europe: results for Switzerland. Mult. Scler. J. 23, 192–203. https://doi.org/10.1177/1352458517708685.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L., Paul, L., 2017. Access, delivery and perceived efficacy of physiotherapy and use of complementary and

alternative therapies by people with progressive multiple sclerosis in the United Kingdom: an online survey. Mult. Scler. Relat. Disord. 12, 64–69. https://doi.org/10.1016/j.msard.2017.01.002.

Dalgas, U, et al., 2019. Exercise as medicine in multiple sclerosis—time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives. Curr. Neurol. Neurosci. Reports 88.

Faraway, J.J., 2002. Practical Regression and Anova Using R. https://doi.org/10.1016/0360-1315(91)90006-D.

Finlayson, M., Plow, M., Cho, C., 2010. Use of physical therapy services among middle-aged and older adults with multiple sclerosis. Phys. Ther. 90, 1607–1618. https://doi.org/10.2522/ptj.20100072.

Henze, T., 2004. Symptomatische Therapie Der Multiplen Sklerose. PsychoNeuro. https://doi.org/10.1055/s-2004-831085.

Henze, T., Feneberg, W., Flachenecker, P., Seidel, D., Albrecht, H., Starck, M., Meuth, S. G., 2018a. What is new in symptomatic MS treatment: part 3—bladder dysfunction. Nervenarzt 89, 184–192. https://doi.org/10.1007/s00115-017-0440-x.

Henze, T., Feneberg, W., Flachenecker, P., Seidel, D., Albrecht, H., Starck, M., Meuth, S. G., 2018b. New aspects of symptomatic MS treatment: part 5 – fatigue. Nervenarzt 89, 446–452. https://doi.org/10.1007/s00115-017-0442-8.

Henze, T., Feneberg, W., Flachenecker, P., Seidel, D., Albrecht, H., Starck, M., Meuth, S. G., 2017. What is new in symptomatic MS treatment: Part 2—gait disorder and spasticity. Nervenarzt 88, 1428–1434. https://doi.org/10.1007/s00115-017-0439-3.

Kaufmann, M., Puhan, M.A., Kuhle, J., Yaldizli, Ö., Magnusson, T., 2019. A framework for estimating the burden of chronic diseases : design and application in the context of multiple sclerosis 10. 10.3389/fneur.2019.00953.

Kaufmann, M., Salmen, A., Barin, L., Puhan, M.A., Calabrese, P., Kamm, C.P., Gobbi, C., Kuhle, J., Manjaly, Z.-M., Ajdacic, V., Schafroth, S., Bottignole, B., Ammann, S., Zecca, C., D'Souza, M., von Wyl, V., 2020. Development and validation of the self-reported disability status scale (SRDSS) to estimate EDSS-categories. Mult. Scler. Relat. Disord. 0, 102148 https://doi.org/10.1016/j.msard.2020.102148.

Kesselring, J., Beer, S., 2005. Symptomatic therapy and neurorehabilitation in multiple sclerosis. Lancet Neurol. 643–652.

Khan, F., Amatya, B., 2017. Rehabilitation in multiple sclerosis: a systematic review of systematic reviews. Arch. Phys. Med. Rehabil. 98, 353–367. https://doi.org/10.1016/j.apmr.2016.04.016.

Milivojević, I., Adamec, I., Habek, M., 2013. Utilization of physical rehabilitation among people with multiple sclerosis. Ir. J. Med. Sci. 182, 429–432. https://doi.org/10.1007/s11845-013-0905-2.

Osborn, R., Squires, D., Doty, M.M., Sarnak, D.O., Schneider, E.C., 2016. In new survey of eleven countries, us adults still struggle with access to and affordability of health care. Health Aff. 35, 2327–2336. https://doi.org/10.1377/hlthaff.2016.1088.

Paltamaa, J., Sjögren, T., Peurala, S.H., Heinonen, A., 2012. Effects of physiotherapy interventions on balance in multiple sclerosis : a systematic review and meta-analysis of randomized controlled trials. J. Rehabil. Med. 44, 811–823. https://doi.org/10.2340/16501977-1047.

Puhan Milo, A., Nina, S., Christian, K., Stefanie, M., Jens, K., Roland, K., Pasquale, C., Jürg, K., Wyl Viktor, V., 2018. A digitally facilitated citizen-science driven approach accelerates participant recruitment and increases study population diversity. Swiss Med. Wkly. 148, 1–8. https://doi.org/10.4414/smw.2018.14623.

Riemenschneider, M., et al., 2018. Is there an overlooked "window of opportunity" in MS exercise therapy? Perspectives for early MS rehabilitation. MSJ 24, 886–894.

Rubin, D.B., 1996. Multiple imputation after 18+ years. J. Am. Stat. Assoc. 91, 473–489. https://doi.org/10.1080/01621459.1996.10476908.

Steinemann, N., Kuhle, J., Calabrese, P., Kesselring, J., Disanto, G., Merkler, D., Pot, C., Ajdacic-Gross, V., Rodgers, S., Puhan, M.A., von Wyl, V., Anderseck, B., Chan, A., Engelhardt, B., Gobbi, C., Häussler, R., Kamm, C.P., Kägi, S., Kurmann, R., Lotter, C., Luyckx, K., Monin, P., Müller, S., Nedeltchev, K., Rapold, I., Salmen, A., Schippling, S., Vaney, C., 2018. The Swiss Multiple Sclerosis Registry (SMSR): study protocol of a participatory, nationwide registry to promote epidemiological and patient-centered MS research. BMC Neurol. 18, 1–10. https://doi.org/10.1186/s12883-018-1118-0.

Toosy, A., Ciccarelli, O., Thompson, A., 2014. Symptomatic treatment and management of multiple sclerosis. Handbook of Clinical Neurology, 1st ed. Elsevier B.V. https://doi.org/10.1016/B978-0-444-52001-2.00023-6

Vos, T., Allen, C., Arora, M., Barber, R.M., Brown, A., Carter, A., Casey, D.C., Charlson, F. J., Chen, A.Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D.J., Dilegge, T., Erskine, H.E., Ferrari, A.J., Fitzmaurice, C., Fleming, T., Forouzanfar, M.H., Fullman, N., Goldberg, E.M., Graetz, N., Haagsma, J.A., Hay, S.I., Johnson, C.O., Kassebaum, N.J., Kawashima, T., Kemmer, L., Khalil, I.A., Kyu, H.H., Leung, J., Lim, S.S., Lopez, A.D., Marczak, L., Mokdad, A.H., Naghavi, M., Nguyen, G., Nsoesie, E., Olsen, H., Pigott, D.M., Pinho, C., Rankin, Z., Reinig, N., Sandar, L., Smith, A., Stanaway, J., Steiner, C., Teeple, S., Thomas, B.A., Troeger, C., Wagner, J.A., Wang, H., Wanga, V., Whiteford, H.A., Zoeckler, L., Alexander, L.T., Anderson, G.M., Bell, B., Bienhoff, K., Biryukov, S., Blore, J., Brown, J., Coates, M.M., Daoud, F., Estep, K., Foreman, K., Fox, J., Friedman, J., Frostad, J., Godwin, W.W., Hancock, J., Huynh, C., Iannarone, M., Kim, P., Kutz, M., Masiye, F., Millear, A., Mirarefin, M., Mooney, M.D., Moradi-Lakeh, M., Mullany, E., Mumford, J.E., Ng, M., Rao, P., Reitsma, M.B., Reynolds, A., Roth, G.A., Shackelford, K.A., Sivonda, A., Sligar, A., Sorensen, R.J.D., Sur, P., Vollset, S.E., Woodbrook, R., Zhou, M., Murray, C.J.L., Ellenbogen, R.G., Kotsakis, G. A., Mock, C.N., Anderson, B.O., Futran, N.D., Jensen, P.N., Watkins, D.A., Bhutta, Z. A., Nisar, M.I., Akseer, N., Abajobir, A.A., Knibbs, L.D., Lalloo, R., Scott, J.G., Alam, N.K.M., Gouda, H.N., Guo, Y., McGrath, J.J., Jeemon, P., Dandona, R., Kumar, G.A., Gething, P.W., Bisanzio, D., Deribew, A., Ali, R., Bennett, D.A., Rahimi, K., Kinfu, Y., Duan, L., Li, Y., Liu, S., Jin, Y., Wang, L., Ye, P., Liang, X., Azzopardi, P., Gibney, K. B., Meretoja, A., Alam, K., Borschmann, R., Colquhoun, S.M., Patton, G.C., Weintraub, R.G., Szoeke, C.E.I., Ademi, Z., Taylor, H.R., Lozano, R., Campos-Nonato, I.R., Campuzano, J.C., Gomez-Dantes, H., Heredia-Pi, I.B., Mejia-Rodriguez, F., Montañez Hernandez, J.C., Rios Blancas, M.J., Servan-Mori, E.E., Mensah, G.A., Salomon, J.A., Thorne-Lyman, A.L., Ajala, O.N., Bärnighausen, T., Ding, E.L., Farvid, M.S., Wagner, G.R., Osman, M., Shrime, M.G., Fitchett, J.R.A., Abate, K.H., Gebrehiwot, T.T., Gebremedhin, A.T., Abbafati, C., Abbas, K.M., Abd-Allah, F., Abraham, B., Abubakar, I., Banerjee, A., Benzian, H., Abu-Raddad, L.J., Abu-Rmeileh, N.M., Ackerman, I.N., Buchbinder, R., Gabbe, B., Thrift, A.G., Adebiyi, A. O., Akinyemi, R.O., Fürst, T., Adou, A.K., Afanvi, K.A., Agardh, E.E., Badawi, A., Popova, S., Agarwal, A., Ahmad Kiadaliri, A., Norrving, B., Ahmadieh, H., Yaseri, M., Jahanmehr, N., Al-Aly, Z., Driscoll, T.R., Kemp, A.H., Leigh, J., Mekonnen, A.B., Aldhahri, S.F., Altirkawi, K.A., Alegretti, M.A., Alemu, Z.A., Alhabib, S., Alkerwi, A., Alla, F., Guillemin, F., Allebeck, P., Rabiee, R.H.S., Carrero, J.J., Fereshtehnejad, S. M., Weiderpass, E., Havmoeller, R., Al-Raddadi, R., Alsharif, U., Alvis-Guzman, N., Amare, A.T., Melaku, Y.A., Ciobanu, L.G., Amberbir, A., Amini, H., Karema, C.K., Ammar, W., Harb, H.L., Amrock, S.M., Andersen, H.H., Antonio, C.A.T., Aregay, A. F., Betsu, B.D., Hailu, G.B., Yebyo, H.G., Ärnlöv, J., Larsson, A., Artaman, A., Asayesh, H., Assadi, R., Atique, S., Avokpaho, E.F.G.A., Avokpaho, E.F.G.A., Awasthi, A., Ayala Quintanilla, B.P., Bacha, U., Balakrishnan, K., Barac, A., Barker-Collo, S.L., Mohammed, S., Barregard, L., Petzold, M., Barrero, L.H., Basu, A., Bazargan-Hejazi, S., Beghi, E., Sheth, K.N., Bell, M.L., Huang, J.J., Santos, I.S., Bensenor, I.M., Lotufo, P.A., Berhane, A., Wolfe, C.D., Bernabé, E., Hay, R.J., Roba, H.S., Beyene, A.S., Bhala, N., Fürst, T., Piel, F.B., Steiner, T.J., Bhatt, S., Greaves, F., Majeed, A., Soljak, M., Biadgiligin, S., Bikbov, B., Bjertness, E., Htet, A.S., Boufous, S., Degenhardt, L., Resnikoff, S., Calabria, B., Mitchell, P.B., Brainin, M., Brazinova, A., Majdan, M., Lo, W.D., Shen, J., Breitborde, N.J.K., Buckle, G.C., Butt, Z.A., Lal, A., Carabin, H., Cárdenas, R., Carpenter, D.O., Castañeda-Orjuela, C.A., Castillo Rivas, J., Catalá-López, F., Catalá-López, F., Chang, J., Chiang, P.P., Chibueze, C.E., Chisumpa, V.H., Choi, J.J., Chowdhury, R., Christensen, H., Christopher, D.J., Cirillo, M., Cooper, C., Cortinovis Biotech, M.D., Giussani Biol, G., Perico, D.N., Remuzzi, G., Crump, J.A., Derrett, S., Poulton, R.G., Damtew, S.A., Deribe, K., Hailu, A.D., Giref, A.Z., Haile, D., Jibat, T., Taye, B., Dargan, P.I., das Neves, J., Massano, J., Santos, J. V., Davey, G., Davis, A.C., Newton, J.N., Steel, N., De Leo, D., Del Gobbo, L.C., Dellavalle, R.P., Des Jarlais, D.C., Dharmaratne, S.D., Dhillon, P.K., Ganguly, P., Zodpey, S., Diaz-Torné, C., Dubey, M., Rahman, M.H.U., Ram, U., Singh, A., Verma, R.K., Yadav, A.K., Duncan, B.B., Kieling, C., Schmidt, M.I., Ebrahimi, H., Pishgar, F., Farzadfar, F., Kasaeian, A., Parsaeian, M., Heydarpour, P., Malekzadeh, R., Roshandel, G., Sepanlou, S.G., Rahimi-Movaghar, V., Elyazar, I., Endres, M., Endries, A.Y., Ermakov, S.P., Eshrati, B., Farid, T.A., Khan, A.R., Farinha, C.S.E.S., Faro, A., Feigin, V.L., Te Ao, B.J., Kwan, G.F., Felson, D.T., Fernandes, J.G., Fernandes, J.C., Fischer, F., Shiue, I., Fowkes, F.G.R., Franklin, R.C., Fürst, T., Iyer, V.J., Gankpé, F. G., Gebre, T., Geleijnse, J.M., Gessner, B.D., Ginawi, I.A., Giroud, M., Gishu, M.D., Tura, A.K., Glaser, E., Halasa, Y.A., Shepard, D.S., Undurraga, E.A., Gona, P., Goodridge, A., Gopalani, S. V., Gotay, C.C., Kissoon, N., Kopec, J.A., Pourmalek, F., Goto, A., Inoue, M., Grainger, R., Gupta, R., Gupta, R., Gupta, V., Gutiérrez, R.A., Knudsen, A.K., Norheim, O.F., Hamadeh, R.R., Hamidi, S., Hammami, M., Handal, A. J., Hankey, G.J., Hao, Y., Harikrishnan, S., Haro, J.M., Hoek, H.W., Skirbekk, V., Horino, M., Horita, N., Hosgood, H.D., Hoy, D.G., Huang, H., Iburg, K.M., Innos, K., Kawakami, N., Shibuya, K., Jacobsen, K.H., Jakovljevic, M.B., Javanbakht, M., Jayaraman, S.P., Jayatilleke, A.U., Jee, S.H., Prabhakaran, D., Jiang, Y., Jimenez-Corona, A., Jimenez-Corona, A., Jonas, J.B., Kabir, Z., Kalkonde, Y., Kamal, R., Kesavachandran, C.N., Kan, H., Karch, A., Karimkhani, C., Kaul, A., Keiyoro, P.N., Lyons, R.A., Keren, A., Khader, Y.S., Khan, E.A., Khang, Y.H., Won, S., Khera, S., Tavakkoli, M., Khoja, T.A.M., Khubchandani, J., Kim, C., Kim, D., Kim, Y.J., Skogen, J.C., Savic, M., Kokubo, Y., Kolte, D., McGarvey, S.T., Kosen, S., Koul, P.A., Koyanagi, A., Kravchenko, M., Varakin, Y.Y., Kuate Defo, B., Kucuk Bicer, B., Kudom, A.A., Polinder, S., Kuipers, E.J., Lallukka, T., Shiri, R., Meretoja, T.J., Lam, H., Lam, J.O., Nachega, J.B., Tran, B.X., Langan, S.M., McKee, M., Lavados, P.M., Leasher, J.L., Leung, R., Levi, M., Li, Y., Liang, J., Liu, Y., Phillips, M.R., Lloyd, B.K., Logroscino, G., Looker, K.J., Lunevicius, R., Mackay, M.T., Magdy Abd El Razek, M., Mahdavi, M., Marcenes, W., Meaney, P.A., Margolis, D.J., Martinez-Raga, J., McMahon, B.J., Mehari, A., Tedla, B.A., Memiah, P., Memish, Z.A., Mendoza, W., Mhimbira, F.A., Miller, T.R., Mills, E.J., Mohammadi, A., Monasta, L., Montico, M., Ronfani, L., Morawska, L., Norman, R.E., Werdecker, A., Mueller, U.O., Westerman, R., Paternina Caicedo, A.J., Murdoch, M.E., Seedat, S., Wiysonge, C.S., Nagel, G., Rothenbacher, D., Naheed, A., Naldi, L., Nangia, V., Ngalesoni, F.N., Nguyen, Q.L., Nkamedjie Pete, P.M., Nolla, J.M., Nunes, B.P., Ogbo, F.A., Oh, I., Ohkubo, T., Olivares, P.R., Olusanya, B.O., Olusanya, J.O., Ortiz, A., Ota, E., Park, E., Passos, V. M.D.A., Patten, S.B., Tonelli, M., Pereira, D.M., Perez-Padilla, R., Pesudovs, K., Pillay, J.D., Plass, D., Platts-Mills, J.A., Pond, C.D., Prasad, N.M., Qorbani, M., Radfar, A., Rafay, A., Rahman, M., Rahman, S.U., Rai, R.K., Rajsic, S., Refaat, A.H., Ribeiro, A.L., Rojas-Rueda, D., Roy, A., Sagar, R., Satpathy, M., Tandon, N., Sahathevan, R., Sanabria, J.R., Sanchez-Niño, M.D., Sarmiento-Suarez, R., Sartorius, B., Sawhney, M., Schaub, M.P., Schneider, I.J.C., Silva, D.A.S., Schöttker, B., Schwebel, D.C., Singh, J.A., Shaheen, A., Shaikh, M.A., Sharma, R., Sharma, U., Shin, M., Yoon, S., Sigfusdottir, I.D., Silveira, D.G.A., Singh, O.P., Singh, P.K., Søreide, K., Sliwa, K., Stein, D.J., Soriano, J.B., Sposato, L.A., Sreeramareddy, C.T., Stathopoulou, V., Stovner, L.J., Steinke, S., Stroumpoulis, K., Sunguya, B.F., Swaminathan, S., Sykes, B.L., Tabarés-Seisdedos, R., Takala, J.S., Tanne, D., Terkawi, A.S., Tuzcu, E.M., Thomson, A.J., Thurston, G.D., Tobe-Gai, R., Topor-Madry, R., Topouzis, F., Truelsen, T., Tsala Dimbuene, Z., Tsilimbaris, M., Tyrovolas, S., Ukwaja, K.N., Uneke, C.J., Uthman, O.A., van Gool, C.H., Vasankari, T., Venketasubramanian, N., Violante, F.S., Vladimirov, S.K., Vlassov, V. V., Waller, S. G., Weichenthal, S., White, R.A., Williams, H.C., Wubshet, M., Xavier, D., Xu, G., Yan, L.L., Yano, Y., Yip, P., Yonemoto, N., Younis, M.Z., Yu, C., Zaidi, Z., Zaki, M.E., Zeeb, H., Zuhlke, L.J., 2016. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a

systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1545–1602. 10.1016/S0140-6736(16)31678-6.

White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: Issues and guidance for practice. Stat. Med. 30, 377–399. https://doi.org/10.1002/sim.4067.

Wiles, C.M., Newcombe, R.G., Fuller, K.J., Shaw, S., Furnival-Doran, J., Pickersgill, T.P., Morgan, A., 2001. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 70, 174–179. https://doi.org/10.1136/jnnp.70.2.174.